REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 9-12 and 23-31 are in the case.

Claims 9-12 and 23-31 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Messer *et al*. ("Oral papain in gluten intolerance", Lancet 2 (7993):1022 (1976)) in view of Hausch *et al*. ("Intestinal Digestive Resistance of Immunodominant Gliadin Peptides", Am. J. Physiol. Gastrointest. Liver Physiol., Oct. 2002, 283, G996-G1003) and Dekker *et al*. (WO 02/45524A2). The rejection is respectfully traversed.

In response, and without conceding to the rejection, the three independent claims in the case, namely claims 9-11, have been amended to specify that the proline specific endoprotease is active in the stomach. Thus, claim 9 provides a method of using a proline specific endoprotease to hydrolyse at a pH of below 5.5, proline rich peptides which are brought with celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in a patient's body of proline specific proteases required for breakdown of these peptides. The method comprises administering a dietary supplement or a medicament comprised of the proline specific endoprotease for ingestion by a patient in need thereof, whereby the proline specific endoprotease is active in the stomach. Claim 10 claims a method of using a proline specific endoprotease to produce food which is devoid of celiac related epitopes by digesting food with the proline specific endoprotease, whereby the proline specific endoprotease is active in the stomach. Claim 11 claims a method of using a proline specific endoprotease having a pH optimum below 6.5 by administering the proline

specific endoprotease for ingestion by a patient in need thereof, whereby the patient suffers from celiac disease, a disease associated with the occurrence of celiac disease, or a disease caused by a decreased level in the patient's body of proline specific proteases, and whereby the proline specific endoprotease is active in the stomach.

Support for the proline specific endoprotease being active in the stomach appears in the specification as originally filed, for example, at page 8, line 34, page 9, beginning at line 18, page 12, beginning at line 6, and page 15, line 29 through to page 16, line 4. In addition, Example 8 demonstrates that *Aspergillus niger* proline-specific endoprotease is capable of breaking down proteins in the stomach. No new matter is entered.

On page 8 lines 26-32 of the specification, in the detailed description of the invention, a discussion is presented as to how the prior art has attempted to provide solutions for activity in humans. In particular, it was necessary to break down gluten in the gut rather than the stomach because the prior art enzyme is not active under acidic conditions and is destroyed in the stomach because it possesses a neutral pH optimum, implying instability under acidic conditions of the stomach. The prior art, therefore, attempted to solve the problem by employing a coating for the enzyme.

Messer discloses (first sentence of the 3rd paragraph) that the four enzymes discussed in the paper should act "within the small intestine" (emphasis added). In the next paragraph, Messer discloses that the patient used "enteric-coated" (emphasis added) tablets of crude papain. The term "enteric-coated" means that tablet is acid-protected by a special coating which disappears once the tablet has traveled past the

stomach. Messer clearly leads **away** from the invention as claimed which requires that the proline specific endoprotease is active in the stomach.

Hausch refers to the breakdown of gliadin peptides in the brush-border membrane (BBM - located in the **intestinal** wall) by exo and endopeptidase (Hausch, page G997, left column, lines 13-16). Ordinarily, gliadin oligopeptides are broken down by peptidases located in the BBM of the intestinal enterocytes (Hausch, page G996, right column, last 2 lines from the bottom). BBM derived from human adult intestinal biopsy was used to verify this theory (Hausch, page G997, left column, lines 18-13 from the bottom). The conclusion is reached that:

> "Although PEP is expressed in human brain, lung, kidney and intestine, no such activity has been reported in the BBM to our knowledge." (Hausch, page G1002 left column, line 34)

Based on this, the suggestion is made:

> "Therefore, we suggest that supplementation of the celiac diet with bioavailable PEP….may be useful in attenuating or perhaps even eliminating the inflammatory response to gluten." (Hausch, page G1002, left hand column, line 37).

Hausch thus suggests use of PEP for breakdown of these gliadin peptides in the BBM or in the intestine. Hausch, therefore, like Messer, leads **away** from the claimed invention which requires that the proline specific endoprotease is active in the stomach.

The corresponding patent application of Hausch *et al*. (WO03/068170) further confirms this point. Hausch '170 mentions enteric formulations with an enteric coating (page 3, line 1 and lines 7-14), and further states that the glutenase should be stabilized

to resist the digestion of the stomach (page 3, lines 3-5). The intention of this coating is to deliver the enzyme to the intestine. Thus, Hausch states:

> "Such formulations include formulations in which the glutenase is contained within an enteric coating that allows delivery of the active agent to the intestine and formulations in which the active agents are stabilized to resist digestion in acidic stomach conditions." (Hausch, page 3, lines 11-14).

Hausch clearly leads away from the claimed invention.

Dekker is relied upon for an alleged disclosure of an enzyme (a prolyl endoprotease) that can hydrolyze proline-rich peptides that are associated with celiac disease at a pH of below 5.5, or that has a p11 optimum below 6.5. However, Dekker describes the use of proline specific endoprotease *in vitro* rather than *in vivo*. While reference is made to reducing allergenicity of food (Dekker, page 7 lines 28-32), the enzyme is incubated with the food proteins prior to consumption. It would appear that enzymes used in this way are killed off during food preparation rather than during food digestion. Dekker is irrelevant to the method as claimed.

Based on the above, it is clear that one of ordinary skill, as of the filing date of the present case, would not have been motivated to rely on Messer and/or Hausch as both of those references focus on the intestine and lead **away** from the method as claimed. Dekker is irrelevant for the reasons discussed above. The cited art, taken singly or in combination, thus does not give rise to a *prima facie* case of obviousness.

As yet further evidence of patentability of the claimed invention, attention is drawn to results described in two articles in well-known scientific publications. These are Stepniak *et al*. published in *Am. J. Physiol. Gastrointest. Liver Physiol.* (Stepniak)

and Mitea *et al.*, published in *Gut* (Mitea). Luppo Edens is named as a co-author on both publications. Copies of the two papers are attached.

Stepniak describes highly efficient gluten degradation using the *Aspergillus niger* proline specific endoprotease. Mitea demonstrates the efficacy of the enzyme (AN-PEP) towards destroying the toxic gluten epitopes in a validated dynamic system closely matching the human gastrointestinal tract (TIM system). In the latter test, a slice of bread as well as a whole fast food menu were introduced into the dynamic system (Mitea, page 25, left hand column, Abstract). These results demonstrate unexpected benefits arising out of the invention as presently claimed.

Withdrawal of the obviousness rejection is respectfully requested.

Respectfully submitted,

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Attachments: Stepniak *et al.*, *Am. J. Physiol. Gastrointest. Liver Physiol.*, 291: G621-G629, 2006, and Mitea *et al.*, *Gut.*, 2008, 57: 25-32.